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Title: The Relationship between Ambient Air Pollution and Heart Rate Variability (HRV) Differs for Individuals with Heart and Pulmonary Disease

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Abbreviations

ACE	angiotensin converting enzyme inhibitors
ASACA	Assessment of Spatial Aerosol Composition in Atlanta
BMI	body mass index
CI	confidence interval
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
EC	elemental carbon
ECG	electrocardiogram
FEV1	forced expiratory volume in one second
FT	Fort McPherson
HF	high frequency power
HR	heart rate
HRV	heart rate variability
IQR	interquartile range
JST	Jefferson St. SAM site
LF	low frequency power
LME	linear mixed effect models
MI	myocardial infarction
NO_2	nitrogen dioxide
O_3	ozone

PM	particulate matter
$PM_{2.5}$	particulate matter < 2.5 μm aerodynamic diameter
PNN50	percent of adjacent RR intervals more than 50 msec different from each other
r-MSSD	square root of the mean of the squared differences between adjacent normal NN intervals
SAM	stationary ambient monitoring
SD	standard deviation
SEARCH	Southeastern Aerosol Research and Characterization
SDNN	standard deviation of normal RR Intervals
SO_2	sulfur dioxide
TEOM	Tapered Element Oscillating Microbalance
TU	Tucker
YRK	Yorkville

Abstract

Associations between ambient fine particle ($PM_{2.5}$) concentrations and heart rate variability (HRV) have differed by study population. We examined the effects of ambient pollution on HRV for 18 individuals with chronic obstructive pulmonary disease (COPD) and 12 individuals with recent myocardial infarction (MI) living in Atlanta, GA. HRV, baseline pulmonary function and medication data were collected for each participant on seven days in either or both Fall 1999 and Spring 2000. Hourly ambient pollution concentrations were obtained from monitoring sites in Atlanta. The association between ambient pollution and HRV was examined using linear mixed effects models (LME). Ambient pollution had opposing effects on HRV in our COPD and MI participants, resulting in no significant effect of ambient pollution on HRV in the entire population for 1-,4-, or 24-hour moving averages. For individuals with COPD, inter-quartile range (IQR) increases in 4-hour ambient $PM_{2.5}$ (11.65 ug/m^3) and NO_2 (11.97 ppb) were associated with 8.3% (95% CI: 1.7, 15.3%) and 7.7% (95% CI: 0.1, 15.9%) increase in the standard deviation of normal RR intervals (SDNN), respectively. For individuals with MI, IQR increases in 4-hr $PM_{2.5}$ (8.54 ug/m^3) and NO_2 (9.25 ppb) were associated with a non-significant 2.9% (95% CI: -7.8, 2.3) and significant 12.1 (95% CI: -19.5, -4.0) decrease in SDNN. Beta-blocker and bronchodilator intake and baseline FEV_1 modified the PM-SDNN association significantly, with effects consistent with those by disease group. Results indicate heterogeneity in the autonomic response to air pollution due to differences in baseline health, with significant associations for ambient NO_2 suggesting an important role for traffic-related pollution.

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Introduction

Recent epidemiological studies have shown associations between ambient particle concentrations and changes in heart rate variability (HRV), a measure of autonomic function. In panel studies of healthy senior citizens (Creason et al. 2001; Gold et al. 2000), cardiac patients (Liao et al. 1999; Pope et al. 1999) and healthy, adult boilermakers (Magari et al. 2001), airborne particles were associated with decreased heart rate variability a known risk factor for sudden death. Conflicting results were found in a study of seniors with chronic obstructive pulmonary disease (COPD), which showed no associations between HRV and PM_{10} and $PM_{2.5}$ (Brauer et al. 2001), and in a study of healthy, young highway patrolmen, which showed strong increases in HRV with $PM_{2.5}$ exposures (Riediker et al. 2004). Results from these studies suggest that compromised autonomic control of the heart may play a role in the acute cardiovascular toxicity of particles but that this role may differ with the underlying health status of the individual. The impact of health status on the relationship between HRV and ambient PM, however, has not been examined directly, with panel studies conducted to date including participants of only one susceptible disease group. To examine this issue more directly, we conducted a study to evaluate associations between ambient fine particles and HRV for sensitive individuals and examine whether these associations differed for individuals with pre-existing pulmonary disease as compared to those with cardiovascular disease.

Methods

In Fall 1999 and Spring 2000, repeated health and exposure measurements were made under a Harvard School of Public Health Human Subjects Committee approved protocol. Measurements were made for individuals living in metropolitan Atlanta who had a myocardial infarction (MI) 3-12 months prior to the start of the study or had self-reported, physician-diagnosed moderate-to-severe COPD. Each of these individuals provided informed consent to participate in the study. Data for this analysis were collected as part of a more comprehensive investigation designed to examine the cardiovascular health effects of fine particles. Measurements were made for each participant over seven consecutive days in one or both seasons, with health measurements made each morning and exposure measurements made each day, beginning 24-h prior to the health measurements. Five participants were monitored simultaneously each seven-day period. Twenty-four and 22 individuals participated in the fall and spring, respectively, with 13 individuals (6 with MI, 7 with COPD) participating in both seasons. A total of 30 individuals – 12 individuals with a recent MI and 18 individuals with COPD – participated in the study.

Participant Recruitment and Baseline Health Assessment

Participants were recruited from a number of locations in the metropolitan Atlanta area; the primary method for recruitment was through physician clinics and rehabilitation centers. Once the individual had expressed interest in participating and their primary care physician had granted approval several screening procedures were undertaken. These included questionnaires on medical history, medication use, housing characteristics, vitamin use, baseline spirometry and a resting 12-lead ECG were also performed (MAC6, Marquette Medical Systems Inc, Milwaukee, WI). Exclusion criteria were similar to the Boston HRV study conducted by Gold et

al. (2000) and included unstable angina, atrial flutter, atrial fibrillation, paced rhythm, left bundle branch block, on constant oxygen, smokers, or living with smokers and inability to walk on level ground. Two participants were unable to complete successfully the pulmonary function maneuver; as a result, baseline spirometry measurements were obtained for 29 of the 30 participants.

Health Monitoring

Field technicians visited participants in their home between 7am and 11am on each monitoring day. At the beginning of each visit, field technicians administered a questionnaire on health status, medication use, vitamin intake, housing characteristics and activity patterns. Field technicians subsequently placed a Holter monitor (SEER MC ambulatory digital analysis recorder, GE Medical Systems, Milwaukee, WI) on each participant and led the participant through a standardized HRV protocol.

The HRV protocol that was followed included continuous Holter monitoring using electrodes in a modified V5 and AVF position. The participant also wore a blood oximeter throughout the protocol (N-20P Oximeter, Nellcor, CA). While wearing these devices, participants were asked to follow a standardized protocol (Gold et al. 2000), in which they were asked to rest in the supine position for five minutes, stand for five minutes, walk outside for five minutes, rest in the supine position for five minutes, and finally to perform paced breathing (5 seconds inhalation and 5 seconds exhalation) for 20 5-second cycles while coached by a technician. The paced breathing portion of the protocol was designed (1) to evaluate whether the effects of pollution on HRV were independent of respiratory rate, which might also be influenced by pollution levels

and (2) to bring out vagal tone in the assessment of HRV. This standardized protocol has been used in other studies specifically for the evaluation of HRV (Sullivan 2005). During each of the five-minute protocol portions, respiratory rate was measured, followed by two blood pressure readings using an automated blood pressure machine (NIBP Vital Signs Monitor, Welch Allyn, NY). The blood pressure readings during the standing portion of the protocol were taken after 2 minutes of standing had elapsed. After the outdoor exercise, the order of the blood pressure readings and respiratory rate was reversed.

The Holter tapes were analyzed using a Marquette MARS Workstation, with a 125 samples/second sampling rate, which is standard for routine HRV analyses and is "satisfactory" under the HRV Guidelines (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. 1996). All analyses were reviewed by a trained technician for noise and artifact. Ectopic beats were excluded in these analyses, with a linearly interpolated QRS based on the prior beat's RR interval and the subsequent beat's RR interval inserted, as is standard. Holter tapes were analyzed for several measures of HRV, including both time and frequency domain outcomes. Time domain outcomes included the standard deviation of normal RR intervals (SDNN), the square root of the mean of the sum of squares of differences between adjacent NN intervals (RMSSD), and the percent of the absolute differences between successive normal R-R intervals that exceed 50ms (PNN50). Frequency domain variables included high frequency power of 0.15 – 0.40Hz (HF) and low frequency power of 0.04 – 0.15Hz (LF).

A total of 300 Holter monitoring sessions were completed for 31 subjects, 28 of whom had 5 or more measurements. Of the 300 observations, 25 observations were excluded due to onset of atrial fibrillation, 3 due to second-degree block, and 3 were unreadable. One participant was subsequently excluded from all analyses due to atrial fibrillation. Of the 300 valid Holter sessions, 3 sessions were missing portions of the overall protocol. These sessions were not excluded from subsequent data analyses, as results did not differ based on their inclusion in the model.

Pollution Measurements

Hourly pollution and meteorological data were obtained from sites located within the metropolitan Atlanta area that were operated as part of other studies (Figure 1). Hourly ambient fine particle ($PM_{2.5}$) concentrations were measured at the Yorkville (YRK), Fort McPherson (FT) and Tucker (TU) stationary ambient monitoring (SAM) sites which were operated as part of the Assessment of Spatial Aerosol Composition in Atlanta (ASACA) and Southeastern Aerosol Research and Characterization (SEARCH) studies (National Research Council, 1999). Sites were located throughout the metropolitan Atlanta area and were characterized by a variety of land uses. TU is classified as a suburban/commercial site, YRK as a rural site, and FT as an urban site. Hourly $PM_{2.5}$ concentrations were measured at these sites using a TEOM with a Nafion dryer placed upstream of the inlet (R & P, Albany, NY). Hourly ozone (O_3) concentrations were measured using EPA approved methods at SAM sites located at TU, YRK, and South Dekalb (SD), a suburban site, while hourly carbon monoxide (CO), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) concentrations were measured using EPA approved methods at the Tucker and SD sites. Black carbon concentrations were measured using aethalometers at the

Jefferson Street (JST) SAM site located in downtown Atlanta in a mixed industrial and residential site that was operated as part of the Aerosol and Inhalation Epidemiological Study (ARIES) network. Meteorological data, including temperature and relative humidity, were also obtained from the JST SAM site. .

Analyses were conducted using three exposure periods – the hour during the recorded HRV protocol and the 4-and 24-hour mean prior to the HRV protocol. Calculated 4- and 24-h mean exposures were considered valid when more than 3 or 18 hours (75% of the hours) were available, respectively. Since participant homes and SAM sites were located throughout metropolitan Atlanta, the average concentration for the available SAM sites was used as the $PM_{2.5}$ and gaseous exposure measure. Exposure data were void if data were only available from one SAM site. Under these criteria, 100%, 84%, 89%, 91% and 95% of the observations were valid for 4-hour exposures to $PM_{2.5}$, NO_2, CO, SO_2, and O_3, respectively.

Data Analysis

The association between ambient pollution and HRV (for the entire 35-minute period) was examined using linear mixed effect models (LME). The heart rate variability outcomes measured in the models were log transformed. Models controlled for time, meteorological, and subject-related variables, including random effects for subjects, and adjusting for BMI, temperature and relative humidity as continuous variables and sex, age, medication use, season, hour and day of week as categorical variables. Medication use was included as a categorical variable for four medication types: beta-blockers, calcium channel blockers, angiotensin converting enzyme

(ACE) inhibitors, and bronchodilators (non-steroidal long and short-acting), with values based on whether the participant was or was not prescribed the medication. As the relationship between weather and the outcome variables were non-linear, both temperature and relative humidity were modeled using natural spline functions with 3 degrees of freedom. Models did not control for heart rate, which is inversely associated with heart rate variability. When heart rate was included in the model, model results were similar, although with slightly lower coefficients.

To identify factors that modify the association between HRV and ambient pollution, parameters, including disease status, baseline pulmonary function, medication use, respiratory rate (RR), air conditioning use, exercise during the protocol, body-mass index (BMI), age and heart rate, were included separately in models. Medication use was controlled for in these models, with the exception of models examining effect modification by medication use. Since only individuals with COPD took bronchodilator medications, models that were stratified by disease status did not control for bronchodilator medications. Analyses of pollution and HRV were conducted with data combined across seasons. All statistical analyses were conducted using S-Plus. Unless otherwise indicated, statistical significance was determined based on a p-value of 0.05.

Results

Participant Profiles

Measurements were obtained for 30 individuals, 12 with recent MIs (3-6 months post-MI) and 18 with self-reported, physician-diagnosed moderate-to-severe COPD. In total, 265 observations were obtained over all participants, 159 for those with COPD and 106 for those

with a recent MI. Participants lived throughout metropolitan Atlanta (Table 1). As shown on Table 1, the COPD participants were generally older, with a higher percentage of females compared with the MI cohort. As would be expected, the COPD cohort had lower baseline lung function (FEV_1). Medication use differed by disease group, with bronchodilators taken only by individuals with COPD and beta-blockers taken by a higher fraction of individuals with a recent MI. Fewer COPD participants were never smokers.

Ambient Pollution Concentrations

Ambient pollution levels varied substantially across the monitoring period (Table 2), with similar distributions for the fall and spring monitoring seasons. Distributions of 1- (not shown) and 24-hour ambient pollution concentrations were comparable to corresponding 4-h values. Four-hour $PM_{2.5}$ concentrations were significantly correlated with 4-h NO_2 ($r=0.44$, $p<0.001$) and CO ($r=0.43$, $p<0.001$) concentrations in both seasons, with correlations strongest in the fall for both pollutants. In both seasons, 4-h $PM_{2.5}$ concentrations were also significantly correlated with corresponding EC levels ($r=0.51$, $p<0.001$). Correlations were also strong among 4-h ambient EC, NO_2, and CO concentrations ($r_{EC\text{-}NO2}$: 0.67, $p<0.001$; $r_{EC\text{-}CO}$: 0.59, $p<0.001$; $r_{NO2\text{-}CO}$: 0.46, $p<0.001$), likely due to the fact that motor vehicles are the major source for these pollutants outdoors.

For $PM_{2.5}$, 4-h mean concentrations were lowest at the rural YRK site (13.2±7.6 ug/m^3) as compared to the TU (21.9±10.5 ug/m^3) and FT (18.5±9.1 ug/m^3) SAM sites. Despite these differences, their concentrations were strongly correlated, with Spearman correlation coefficients exceeding 0.75 for comparisons among the SAM sites and exceeding 0.89 for comparisons of the

individual site concentrations with the mean concentration across the sites. Although mean 4-h concentrations were comparable across sites, correlations among the sites' 4-h NO_2 concentrations more moderate, but remained significant, with a Spearman correlation coefficient for a comparison of TU and SD concentrations of 0.44 and coefficients for comparisons with the mean NO_2 concentration across the two sites greater than 0.72. Four hour mean O_3 concentrations differed substantially across the sites, with mean levels highest at YRK (33.8±12.6 ppb), followed by TU (14.5±10.5 ppb) and SD (8.0±9.2 ppb) sites. Correlations among the sites were also weaker, primarily due to the low correlations observed for the rural YRK site (0.30 and 0.00 for YRK-TU and YRK-SD comparisons, respectively).

For EC, since hourly ambient EC concentrations were measured at only the JST SAM site, spatial variability was evaluated using 24-h ambient EC concentrations measured at the Yorkville and JST SAM sites. The mean 24-h concentration at JST (1.81±1.06 ug/m^3) was approximately twice that for YRK (0.77±0.45 ug/m^3), which is consistent with the fact that JST was located in an urban/suburban area and Yorkville was located in a rural area. Despite these differences in mean levels, 24-h EC concentrations at these sites were moderately correlated during the study period, with a significant Spearman correlation of 0.47.

HRV Outcomes

Several of the HRV outcomes were found to vary significantly by disease group (Table 3). Individuals with COPD, for example, had significantly lower SDNN and LF values as compared to individuals with a recent MI as determined using the Wilcoxon rank sum test (p =0.012 and 0.0003, respectively). Heart rate, a potential modifier of HRV, was lower in the MI group

($p<0.0001$), which may reflect beta-blocker use in the MI cohort. For all other outcomes, comparable values were found across disease group.

Association between $PM_{2.5}$ and HRV

The association between ambient $PM_{2.5}$ and the standard deviation of normal RR intervals (SDNN) was positive for individuals with COPD, with associations strongest for the 4-hr moving average (Table 4). For the 4-hr moving average, SDNN rose by 7.5% (95% CI: 1.5 to 13.9%) per inter-quartile range (IQR) increase in ambient $PM_{2.5}$ (10.64 ug/m^3). In comparison, opposing effects of ambient $PM_{2.5}$ on HRV were found in individuals who were post-MI, resulting in no significant overall summary effect of ambient $PM_{2.5}$ on HRV in the entire population for moving averages of 1-, 4-, or 24-hours (Table 4). When these analyses were performed using models that instead included an interaction term between $PM_{2.5}$ and disease status, the disease group-specific effects of ambient $PM_{2.5}$ on HRV were similar to those obtained from our stratified analyses, with a significant interaction term. As shown on Table 5, associations of $PM_{2.5}$ and other HRV measures, r-MSSD, PNN50, LF, HF, and LF/HR, generally followed similar trends by disease status, with associations significant only for LF in individuals with COPD.

Association between HRV and Other Pollutants

4-hour ambient NO_2 concentrations were associated with changes in SDNN when analyses were stratified by disease status (Table 6), with results exhibiting trends consistent with those for ambient $PM_{2.5}$. Effect sizes for NO_2 were similar to those observed for ambient $PM_{2.5}$ for individuals with COPD and were larger and more precise than those observed for ambient $PM_{2.5}$ for individuals with an MI. An IQR increase in 4-hr NO_2 concentrations (10.75 ppb) was

associated with a 6.9% (95% CI: 0.1 to 14.2) increase in SDNN in individuals with COPD and a 13.9% (95% CI: -22.2 to -4.7) decrease in SDNN in persons with a recent MI. For EC, trends consistent with those for ambient $PM_{2.5}$ and NO_2 were observed; however, associations were insignificant. Ambient O_3 concentrations were not associated with SDNN when data were examined for all subjects or were stratified by disease group (Table 6).

Effect Modification by Additional Diagnosis-Related Endpoints. The effect of medication use, respiratory rate (RR), baseline pulmonary function (as measured by FEV_1), air conditioning use, exercise during HRV measurement, BMI, age, and heart rate on the association between 4-hour ambient pollution and overall SDNN was examined to determine whether these factors was responsible for the differences in response between the disease groups. Of these, medication use and baseline FEV_1 were found to be significant effect modifiers for 4-hr $PM_{2.5}$ and NO_2 concentrations, with results comparable for the two pollutants (Table 7). Similar effect modification by medication use and baseline pulmonary function was also found for EC but with smaller effect sizes.

Baseline FEV_1. Consistent with the results by disease group, baseline FEV_1 (% predicted) significantly modified the association between SDNN and 4-h ambient $PM_{2.5}$ and NO_2 among all participants, with the $PM_{2.5}$-SDNN association increasing with decreasing baseline FEV_1. Coefficients for the main pollution effect and the FEV_1 interaction term equaled 0.015 (s.e.=0.004, t-value=3.46) and -0.0002 (s.e.=0.0001, t-value=-3.18), respectively. For individuals with poor pulmonary function (baseline FEV_1 35% of predicted; 10th% for study population), these values corresponded to a 10.2% increase in SDNN for an IQR increase in 4-h

ambient $PM_{2.5}$ concentrations, while for individuals with normal pulmonary function (baseline FEV_1 105% of predicted; 90th% for the study population) these values corresponded to a 2.5% decrease in SDNN for the same IQR increase in $PM_{2.5}$ (Table 7).

Medication Use. Beta-blocker and bronchodilator use on the health measurement day significantly modified the association between 4-h ambient $PM_{2.5}$ and NO_2 concentrations and SDNN (Figure 2). SDNN decreased by 7.3% (95% CI: -13.8 to –0.35) for subjects taking beta-blockers and increased by 5.8% (95% CI: 0.91 to 10.8) for other subjects with an IQR increase in 4-h ambient $PM_{2.5}$. Responses were consistent in direction with those for individuals with an MI and COPD, respectively. Opposite patterns were observed for subjects taking bronchodilator medications, where positive SDNN-$PM_{2.5}$ associations were found for those on the medication and negative associations were found for other subjects. The effect sizes for $PM_{2.5}$-associated changes in SDNN for individuals taking medications were higher in magnitude as compared to effect sizes for corresponding individuals with MI or COPD alone. Medications that were taken by individuals from both disease groups, including ACE inhibitors and calcium channel blockers, were not found to modify the SDNN-$PM_{2.5}$ association significantly.

Effect of Spatial Variability on Effect Estimates. The effect of spatial variability in ambient $PM_{2.5}$ on observed associations between overall SDNN and ambient $PM_{2.5}$ and ambient NO_2 was analyzed using data from each of the individual SAM sites. For $PM_{2.5}$, spatial variability in ambient concentrations had little effect on the observed associations, as both the magnitude and direction of the association between SDNN and 4-h ambient $PM_{2.5}$ was comparable across sites (Table 8). These results are consistent with the strong correlations among the sites' $PM_{2.5}$

concentrations, with Spearman correlation coefficients greater than 0.87 for pair-wise comparisons of the 4-hr concentrations at the individual sites with the 4-hr across site mean concentrations. Results suggest that for $PM_{2.5}$, the mean ambient SAM $PM_{2.5}$ concentration is a good indicator of ambient $PM_{2.5}$ across the metropolitan Atlanta area.

For NO_2, similar trends by disease status were found when associations were estimated using data for the individual SAM sites as compared to the mean of these sites (Table 8). The magnitude and significance of the associations, however, dropped, with associations for individuals with MIs no longer significant when measurements at the South DeKalb site were used in the analysis. These findings suggest greater exposure error when measurements from single SAM sites were used to reflect exposures for our study population.

Discussion

Findings from our study provide direct evidence of heterogeneity in the autonomic response to ambient pollution that is dependent on the underlying health status of the study population. Changes in HRV were significantly and positively associated with ambient $PM_{2.5}$ concentrations for individuals with COPD. Although not statistically significant, observed associations were consistently negative for individuals with recent MI. Further support that the HRV response to ambient $PM_{2.5}$ differs for individuals with MI and COPD was provided by the fact that comparable effect estimates, with significant differences between disease groups, were found using models that included an interaction term between pollution and disease status. Associations

with ambient $PM_{2.5}$ were strongest for the 4-hour moving average and for SDNN, an overall measure of HRV, although consistent trends with disease status were observed for other moving averages and other HRV measures, including rMSSD, HF, and the HF/LF ratio. Strong and significant associations with SDNN by disease group were also observed with ambient NO_2, and to a lesser extent with ambient EC. Since ambient NO_2 and EC originate primarily from motor vehicles, our findings suggest that motor vehicle-related pollution may be partly responsible for the observed effects of ambient particles on HRV.

Since results were similar irrespective of whether models controlled for heart rate and since heart rate did not modify the $PM_{2.5}$-HRV association, results suggest that the observed effect modification by disease status was due to factors other than differences in heart rate. For individuals with recent MI, the negative, albeit insignificant, association observed between ambient $PM_{2.5}$ and HRV was consistent with previous studies of elderly individuals (Creason et al. 2001; Gold et al. 2000), elderly individuals with preexisting cardiovascular-related conditions (Liao et al. 1999; Liao et al. 2004), and occupationally exposed, middle-aged boilermakers (Magari et al. 2002).

In contrast, our finding of positive associations between $PM_{2.5}$ and HRV for individuals with COPD is in direct contrast to findings from the only other published study of pollution effects on HRV in individuals with COPD, in which HRV was measured repeatedly for 16 individuals with mild-to-moderate COPD ($FEV1 \geq 0.75$ l) living in Vancouver, Canada (Brauer et al. 2001). For these individuals, non-significant ambient $PM_{2.5}$-associated decrements in SDNN and rMSSD were found, with the lack of statistical significance attributed to low ambient pollution levels and

the small sample size. The negative direction of the $PM_{2.5}$-HRV association in Vancouver was comparable in magnitude to that observed in elderly individuals living in Boston (Gold et al. 2000). The contrasting $PM_{2.5}$ and HRV associations for the Vancouver and our COPD cohorts may result from the fact that the Vancouver cohort had less severe pulmonary disease as compared to our cohort (as defined by the self-reported physician diagnoses). Positive associations between HRV and $PM_{2.5}$ have been demonstrated previously in a study of young, healthy cohort of highway patrolmen (Riedeker et al. 2004). For these healthy patrolmen, SDNN increased significantly by 11.7% per 10 ug/m^3 in $PM_{2.5}$ exposures. This increase is comparable to our 7.5% increase for a similar change in ambient $PM_{2.5}$ (10.64 ug/m^3). Positive associations for the patrolmen were attributed to increased vagal activity in the young and healthy cohort.

Cardiovascular autonomic neuropathy is common, though not universal, in patients with COPD (Chhabra 2005). While many patients with COPD have marked baseline sympathetic activation (Heindl 2001), individuals with COPD have been demonstrated to respond to stimuli such as exercise with increased vagal tone as measured by increases in HF (Bartels 2003). It is possible that ambient pollution has similar effects on increases in vagal tone amongst at least some subsets of patients with COPD.

Since our COPD participants were generally older and less active than our MI participants, however, it is difficult to determine whether the observed effect modification by disease group reflect differences in the participant characteristics or in the diseases themselves. Of the patient characteristics, medication use was shown to be an important modifier of the HRV-$PM_{2.5}$ associations. Individuals with COPD and MI were generally prescribed different medications,

with beta-blocker and bronchodilator use was limited largely to individuals with a recent MI and COPD, respectively. Correspondingly, effect estimates for subjects taking beta-blockers exhibited similar trends as those for subjects with an MI, while effect estimates for subjects taking bronchodilators were consistent with those for individuals with COPD. As a result of this strong overlap between medication use and disease group, it is not possible to separate the effects of medication use from disease in this study.

Baseline pulmonary function, as measured using baseline FEV_1, was also found to modify the association between ambient $PM_{2.5}$ and SDNN. From our linear model estimating the modification of $PM_{2.5}$ effects by level of FEV_1, we estimate that the $PM_{2.5}$-HRV association decreased significantly with increasing pulmonary function, comparable to a 10.2% increase in SDNN for an IQR change in ambient $PM_{2.5}$ for individuals with poor pulmonary function (baseline FEV_1 35% of predicted) and a 2.5% decrease in SDNN for individuals with normal lung function (baseline FEV_1 105% of predicted). Since the baseline pulmonary function was normal and narrowly distributed for individuals with recent MI, the observed impact of baseline pulmonary function on the $PM_{2.5}$-SDNN response largely reflects variation in baseline pulmonary function among individuals with COPD. Since the influence of baseline pulmonary function on HRV was not examined in previous studies, it is unknown whether baseline pulmonary function had similar impacts on the PM-associated HRV response in the previously reported studies. Evidence from cardiovascular health studies, however, suggests that respiratory health status may be an important modifier of the pollution-mediated autonomic response, as HRV in individuals with COPD has also been shown to decrease with FEV_1 (Stein et al. 1998).

Negative associations between average HRV and baseline FEV_1, however, were not observed in our COPD cohort.

Results for $PM_{2.5}$ were robust with respect to location of the SAM site, as results were comparable when $PM_{2.5}$ concentrations at individual SAM sites were used as the exposure measure, suggesting that spatial variation in $PM_{2.5}$ was not a significant source of exposure error for our study participants. For NO_2, similar sensitivity results show consistent trends in the NO_2-HRV associations by disease group . Larger differences in the effect estimates, however, were found with different methods to estimate ambient NO_2 exposures, suggesting that exposure error due to spatial variability was greater for NO_2 as compared to $PM_{2.5}$. This greater exposure error is consistent with the fact that traffic, which varies spatially over short distances, is a significant source of outdoor NO_2. Although comparable sensitivity analyses could not be conducted for BC, significant correlations between 24-h concentrations measured at the JST and YRK sites suggest that BC concentrations measured at the JST SAM site were able to reflect BC concentrations across Atlanta. Since these correlations were more moderate as compared to those for $PM_{2.5}$ and were similar in magnitude to those for NO_2, it is likely that spatial variation in outdoor BC levels contributed to error in our exposure estimates and thus may have impacted our observed effect estimates. For both NO_2 and BC, this greater exposure error may explain the lower and insignificant effect estimates found for these pollutants.

One important limitation of this investigation is the small number of individuals studied, with only 18 and 12 individuals with COPD and a recent MI, respectively. Our findings of effect modification by medication use and baseline pulmonary function, COPD and a recent MI,

however, were consistent with our findings of differential susceptibility for individuals with COPD and a recent MI. Further study is needed to identify factors responsible for this differential susceptibility and to identify whether the autonomic response of individuals with other health conditions also differ after ambient pollution exposures.

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Table 1. Participant Characteristics by Disease Status

Participant Characteristic	Disease Group		
	COPD	MI	All[a]
Gender:[b]			
Male	7	10	30
Female	11	2	
Age (years):[c]			
Male	74 (71-76)	59 (49-70)	65 (55-73)
Female	64 (49-75)	69 (66-71)	
FEV_1 (% predicted): [c,d]			
Male	67 (43-80)	99 (86-115)	69 (44-98)
Female	45 (36-59)	96 (91-101)	
Body Mass Index (BMI) [c]	27 (22-31)	27 (25-28)	27 (25-29)
Medication Use: [a,e]			
Beta blockers	1	8	9
Calcium channel blockers	4	3	7
Angiotensin-converting enzyme inhibitors	3	6	9
Bronchodilators– short acting	12	0	12
Bronchodilator – long acting	5	0	5

[a] Totals for all participants
[b] Expressed as number of participants
[c] Expressed as mean and interquartile range (in parentheses)
[d] Does not include data for two participants, for which baseline pulmonary function could not be measured.
[e] Short-acting bronchodilators include ventalin, seravent, albuterol, proventil / HfA, proventil rep, maxair, combivent (includes atrovent), provertic. Long-acting bronchodilators include theodur.

Table 2. Summary of Meteorological and Air Pollution Levels

Parameter[a]	N	Mean	10%	25%	50%	75%	90%	24h[b]
Meteorology (24-h):								
Temp (^{o}C)	265	17.8	12.2	16.1	18.0	20.3	23.6	-
RH (%)	265	70.3	52.5	57.4	70.1	82.6	92.6	-
Pollution (4-h):								
$PM_{2.5}$ (ug/m^3)	264	17.8	7.0	11.6	16.5	22.2	30.9	17.2
EC (ug/m^3)	260	2.3	0.9	1.2	1.6	2.9	4.4	2.0
O_3 (ppb)	251	18.5	9.0	12.7	17.0	22.5	30.3	29.4
CO (ppb)	236	362.0	169.7	221.5	304.3	398.1	682.1	332.1
SO_2 (ppb)	240	1.9	0.7	0.9	1.5	2.4	3.6	2.5
NO_2 (ppb)	222	17.8	7.1	12.0	17.0	22.8	29.8	17.1

[a] Values correspond to the mean for the 24- or 4-hour periods prior to the HRV measurements.
[b] Corresponding 24 hour mean values for time period prior to the health measurements.

Table 3. Heart Rate Variability by Disease Status[a]

HRV Parameter[b]	Mean (10%, 90%)	
	COPD (n=18)	MI (n=12)
SDNN (ms)	104.4 (55.2, 186.2)	114.8 (63.8, 207.4)
RMSSD (ms)	44.5 (14.4, 129.4)	39.2 (12.6, 115.2)
PNN50 (%)	10.0 (0.4, 30.9)	6.4 (0.2, 23.2)
LF (ms^2)	759.1 (62.8, 3700.6)	808.1 (115.5, 2726.2)
HF (ms^2)	333.4 (36.1, 1278.1)	361.0 (49.8, 1356.9)
LF:HF (ms^2/ms^2)	2.5 (1.1, 6.8)	3.7 (0.9, 7.4)
HR (bpm)	80.9 (64.2, 105.7)	68.6 (54.0, 86.7)

[a]Includes data for all participants in both seasons; means and 10th and 90th percentiles expressed as the values for the participant means.

[b]SDNN is the standard deviation of normal RR intervals (SDNN), RMSSD the square root of the mean of the sum of squares of differences between adjacent NN intervals, PNN50 the percent of the absolute differences between successive normal R-R intervals that exceed 50ms, HF high frequency power of 0.15 – 0.40Hz, LF low frequency power of 0.04 – 0.15Hz, and HR the heart rate.

Table 4. Association between Ambient $PM_{2.5}$ and Overall SDNN

$PM_{2.5}$: Integration Period	IQR (ug/m^3)	% Change	95% CI
1 Hour	10.3	1.50	-2.22, 5.36
MI only	9.74	-2.75	-7.93, 2.72
COPD only	10.66	5.07*	0.01, 10.38*
4 Hour	10.63	1.97	-2.30, 6.43
MI only	8.54	-2.89	-7.79, 2.27
COPD only	11.65	8.29*	1.71, 15.30*
24 Hour	8.00	-1.00	-4.67, 2.82
MI only	8.05	-4.38	-9.42, 0.94
COPD only	7.84	1.58	-3.59, 7.01

Percent change in overall SDNN (with 95% confidence intervals) expressed per IQR change in ambient $PM_{2.5}$. Model does not include heart rate. Statistically significant estimates indicated with asterisk.

Table 5. Association between Ambient 4-h $PM_{2.5}$ and Other HRV Parameters

HRV Measure	% Change	95% CI	t-value
SDNN	1.97	-2.30, 6.43	0.90
MI	-2.89	-7.79, 2.27	-1.11
COPD	8.29*	1.71, 15.30	2.49
r-MSSD	-0.92	-10.19, 9.30	-0.18
MI	-11.38	-23.03, 2.03	-1.68
COPD	9.77	-5.37, 27.35	1.23
PNN50	-2.96	-18.15, 15.03	-0.35
MI	-10.18	-29.94, 15.17	-0.85
COPD	-1.19	-21.07, 23,70	0.10
LF	14.04	-1.84, 32.49	1.72
MI	1.12	-15.52, 21.03	0.12
COPD	35.88*	6.79, 72.90	2.49
HF	5.03	-9.96, 22.52	0.62
MI	-6.48	-25.68, 17.70	-0.57
COPD	19.41	-4.05, 48.59	1.59
LF/HF	1.85	-4.91, 9.09	0.52
MI	-1.28	-9.16, 7.28	-0.30
COPD	6.68	-4.02, 18.59	1.20

Percent change in HRV (overall protocol) expressed per IQR change in 4-h ambient $PM_{2.5}$. IQR changes were 10.6, 8.5, and 11.7 ug/m^3 for the 4-h mean of the SAM sites for all, MI, and COPD participants, respectively. Model does not include heart rate. Statistically significant estimates indicated with asterisk. SDNN is the standard deviation of normal RR intervals (SDNN), RMSSD the square root of the mean of the sum of squares of differences between adjacent NN intervals, PNN50 the percent of the absolute differences between successive normal R-R intervals that exceed 50ms, HF high frequency power of 0.15 – 0.40Hz, LF low frequency power of 0.04 – 0.15Hz, and HR the heart rate.

Table 6. Association between 4-h EC, NO_2, and O_3 Concentrations and Overall SDNN

Pollutant	IQR	% Change	95% CI
EC	1.68	-0.83	-3.27, 1.67
MI only	1.39	-1.06	-4.19, 2.16
COPD only	1.92	0.51	-3.33, 4.51
NO_2	10.66	-0.49	-5.4, 4.6
MI only	9.25	-12.09*	-19.5, -4.0
COPD only	11.97	7.70*	0.1, 15.9
O_3	9.61	0.75	-3.6, 5.3
MI only	8.08	0.13	-6.5, 7.2
COPD only	10.66	2.45	-3.4, 8.7

Percent change in overall SDNN (with 95% confidence intervals) expressed per IQR change in pollutant concentrations. Units for IQR are ug/m^3 for EC, and ppb for O_3 and NO_2. Model does not include heart rate. Statistically significant estimates indicated with asterisk.

Table 7. Association of SDNN and Ambient 4-h Concentrations: Baseline FEV_1 (% Predicted) as an Effect Modifier

Pollutant	FEV_1	% Change	95% CI
$PM_{2.5}$ (10.6 μg/m^3)	105	-2.5	(-7.8, 3.2)
	35	10.2*	(3.8, 17.0)
EC (1.7 μg/m^3)	105	-3.9*	(-7.4, -0.3)
	35	2.5	(-1.3, 6.4)
NO_2 (10.7 ppb)	105	-5.4	(-12.0, 1.8)
	35	5.7	(-1.2, 12.9)
O_3 (9.6 ppb)	105	-0.4	(-7.1, 6.8)
	35	1.1	(-4.1, 6.6)

Expressed as a change per IQR for the 4-Hr mean ambient concentration (in parentheses). Statistically significant associations indicated with asterisk.

Table 8. Association between Ambient 4-h $PM_{2.5}$ and SDNN: By SAM Site

Pollutant	SAM Site	IQR	% Change	95% CI	t-value
$PM_{2.5}$	Mean of SAM sites	10.63	1.97	-2.30, 6.43	0.90
	MI	8.54	-2.89	-7.79, 2.27	-1.11
	COPD	11.65	8.29*	1.71, 15.30	2.49
	Tucker	15.40	1.74	-3.2, 6.9	0.68
	MI	14.33	-3.59	-10.3, 3.6	-1.00
	COPD	15.98	7.39*	0.4, 14.9	2.07
	Fort McPherson	13.04	1.13	-3.7, 6.2	0.45
	MI	12.68	-5.35	-11.7, 1.5	-1.55
	COPD	13.78	7.10	0.05, 14.7	1.97
	Yorkville	8.35	2.71	-1.3, 6.9	1.31
	MI	7.99	-3.63	-9.0, 2.0	-1.27
	COPD	8.52	8.23*	2.2, 14.6	2.72
NO_2	Mean of SAM sites	10.66	-0.49	-5.4, 4.7	-0.19
	MI	9.25	-13.88*	-22.1, -4.7	-2.88
	COPD	11.97	6.89*	0.1, 14.2	1.97
	Tucker	13.75	-1.61	-5.9, 2.9	-0.71
	MI	12.88	-10.36*	-17.7, -2.4	-2.53
	COPD	13.75	3.75	-2.1, 10.0	1.24
	South Dekalb	12.06	0.57	-4.7, 6.1	0.21
	MI	11.06	-6.50	-14.6, 2.4	-1.45
	COPD	12.19	4.99	-1.7, 12.2	1.44

Percent change in overall SDNN expressed per IQR change in ambient $PM_{2.5}$. Model does not include heart rate. Statistically significant estimates indicated with asterisk.

Figure 1. Locations of participant's homes and the stationary ambient monitoring sites, Atlanta, GA.

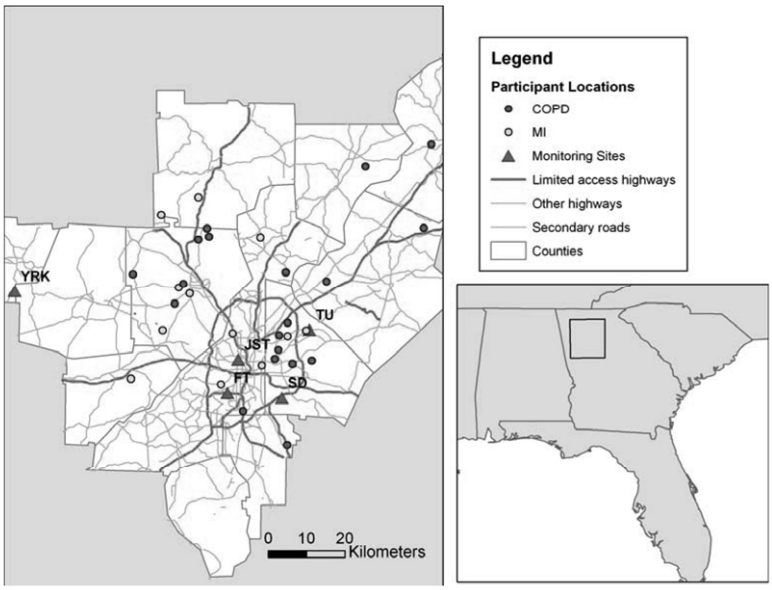
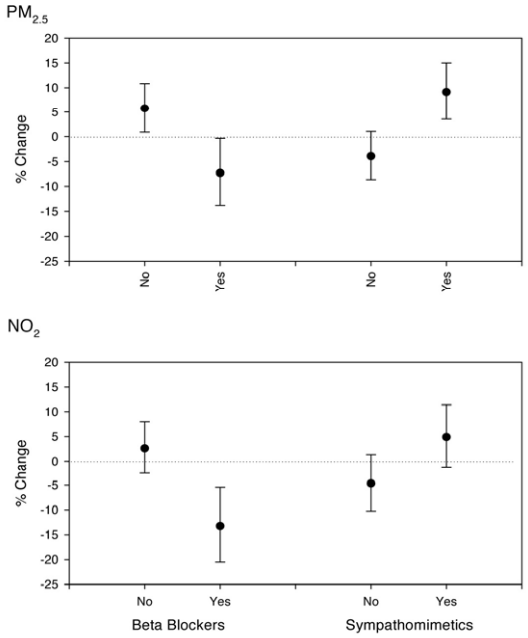


Figure 2. Percent Change in SDNN with 4-h $PM_{2.5}$ and NO_2



[1]Percent change expressed with 95% per IQR change in $PM_{2.5}$ (10.64 ug/m^3) or NO_2 (10.75ppb). Medication use status based on whether participant took medication on the morning of the health measurement. All % changes differed significantly by medication use at the 0.05 level.